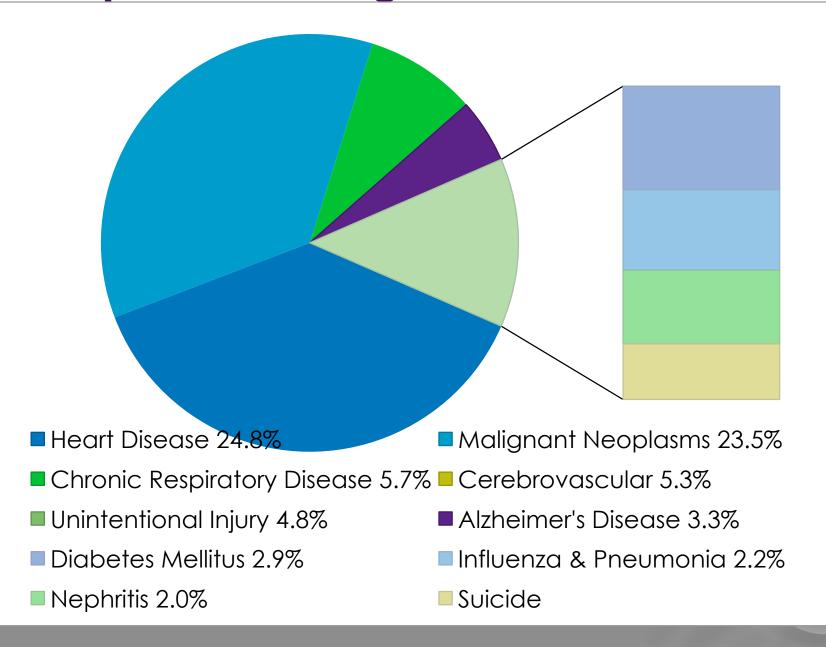


Definitions

➤ **Genetics** – study of individual genes and their impact on relatively rare single gene disorders

➤ Genomics – study of all the genes in the human genome together, including their interactions with each other, the environment, and other psychosocial and cultural factors

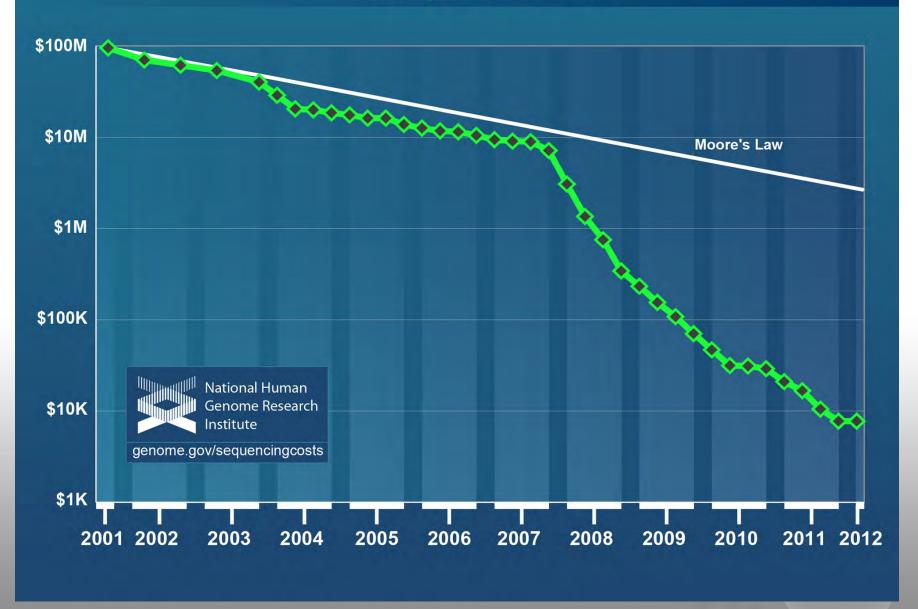
Top 10 Leading Causes of Death



Emerging Science/Technology



Cost per Genome



The Race for the \$1000 Genome

1000 Genomes Project Promises Closer Look at Variation in Human Genome

the genetic basis of disease.

nome reject and use trapparation and technicogues are aboved use tree to ask of decidate their deferming the com-mon patterns of genetic variation in late-mansa), investigations for the 1000 Ge-nomes Project plan to develop an open project plan to develop an nomes Project plan to develop an quence approximately 8.2 billion bases extensive catalog of variation in the huper day—the equivalent of about 2 human genome by sequencing the ge-man genomes every 24 hours. Al-hough the cost of the project has been mentosa has been linked to variatic round the world. The project is being estimated to be between \$30 and \$50 in more than 100 genes; the fact that arried out by an international consor- million, Altshuler noted that a precise all these genes are involved in the photunn of researches, including seats
able because the technological adnome Research Institute in Bethesda,
which the Wellcome Trust Sanger lines
sequencing,
interventions. Md; the Wellcome Trust Sanger Insti-sequencing.

62008 American Medical Association. All rights reserved.

M. Kuenn

jing Genomics Institute in Shenzen,
NEW, LARGE-SCALE PUBLIC SCIChina. The first official data from the ence project is developing a project will be released in January 2009, menting single nucleotide polymor phisms and larger genetic variations NHGRI Funding Opportunities: Resea one day add scientiss' understanding of genetics and medicine at Harvard will produce a database that scientiss' understanding of genetics and medicine at Harvard will produce a database that scientiss Medical School in Boston, Mass. will be able to search for variations in Building on the data and techniogy generated in previous "big seionner Project and the HappMap ion
and Genome Project are liberage for and the HappMap ion
and technologies are allowing the redata to identify disease-causing varia-

tute in Hinxton England and the Rei. The project will reveal variation in

um of researchers, including scien- estimate of cost is not currently avail- totransduction cascade suggests that

[era.nih.gov]. Inquiries about NHGRI's program interests should be addressed to the Division of E.

Mardis Genome Medicine 2010, 2:84 http://genomemedicine.com/content/2/11/84

NHGRI Funding Opportunities

NIH-Wide Parent Funding Opportunities

NIH-Wide Topic-Specific Funding Opportunitie

The National Institutes of Health (NIH) is replacing pa

transition to requiring electronic submission of grant

the electronic application and transition timelines and

Genomics Law Report

News and analysis from the intersection of genomics, personalized medicine and the law

HOME

ABOUT

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Another Stop on the Road to the \$1,000 Genome

Posted by Dan Vorhaus on January 12, 2010

The latest stop on the road to the \$1,000 genome? San Francisco, CA, where J.P. Morgan's 28th Annual Healthcare Conference is in full swing. There is an abundance of realtime Twitter coverage from the conference, but certain announcements warrant a more detailed discussion

The announcement generating the biggest buzz today came from Illumina, Inc., whose CEO Jay Flatley unveiled a new genome sequencing machine, the HiSeq 2000. According to Matthew Herper of Forbes.com, Illumina's new machine "wil

000 worth of mpeting

chines will begin shipping in February with a cost of \$690,000 odel). Illumina's own product page for the HiSeg 2000 age (~30x) and read length (2×100 bp). There have also been equipped with an iPhone user interface, a concept that Flatley

cs Show



MUSINGS

Program Staff

The \$1,000 genome, the \$100,000 analysis?

Elaine R Mardis*

Having recently attended the Personal Genomes meeting at Cold Spring Harbor Laboratories (I was an organizer this year), I was struck by the number of talks that described the use of whole-genome sequencing and analysis to reveal the genetic basis of disease in patients.

required for it to occur. I therefore offer the following as food for thought.

One source of difficulty in using resequencing approaches for diagnosis centers on the need to improve the quality and completeness of the human reference

Direct to Consumer Marketing and Testing

- Tests available direct to the consumer without an ordering healthcare provider
 - Varied test types
 - High penetrance diseases
 - Polygenic diseases
 - Risk Assessment
 - Low penetrance genes
 - Enhancement tests
 - Pharmacogenomic
 - Nutrigenomic
- >Most require only a saliva sample
- Costs vary based on test but can be as low as \$99

Consumer Perspectives on DTC

- 1,087 Facebook users, aged 18-81, mean 35
- 47% were aware of personal genetic testing (PGT)
- 6% had used PGT
- 64% indicated that they would consider using PGT
- 34% mistakenly understood that results of PGT results indicated a diagnosis of disease
- 78% would consult their physicians to interpret PGT results

McGuire AL, Diaz CM, Wang T, et al.: Social networkers' attitudes toward direct-to-consumer personal genome testing. Am J Bioeth 9 (6-7): 3-10, 2009.

Scope of Genome Analysis

- Has expanded to include any whole genome analysis such as
 - Whole genome sequencing
 - Whole exome sequencing
 - RNA and RNAi sequencing
 - Whole genome SNP analysis
- Consideration for incidental findings
 - Previously unknown information
 - Clinical and analytic validity of finding
 - Immediacy and seriousness of risk
 - Actionable finding
 - Timing
 - Confirmation in CLIA approved laboratory

Research Ethical Considerations

- >Stability of DNA
 - Storage and future use
- ▶ Broad sharing of samples/data
- >Limited control of downstream use
- >Limited right to withdraw
- >Identifiability
- >Incidental findings
 - Duty to re-contact
- >Implications for family/community

Green, R.C., et al. (2013). ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing. http://www.acmg.net/docs/ACMG_Releases_Highly-Incidental_Findings_in_Clinical_Exome_and_Genome_Sequencing.pdf Wolf, S., et al. (2012). Managing incidental findings and research results in genomic research involving biobanks and archived data sets. Genetics in Medicine, 14, 361-384 Rodriguez, L.L., et al. (2013). Research ethics: The complexities of genomic identifiability. Science, 339, 275-6.

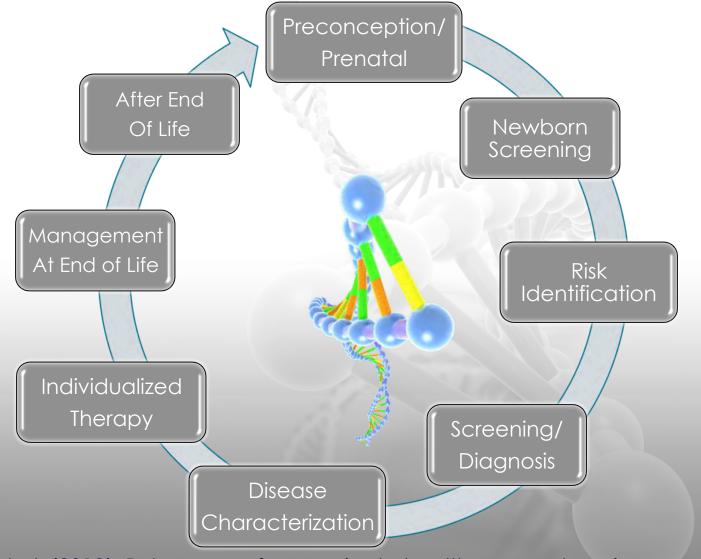
Incidental Findings, Public Perspectives

- 89 individuals from 10 focus groups
- Nearly all would want individual research results (IRR) returned
 - Priority on results that are well understood
 - Magnitude of the risk and actionability was less important
- Reasons to obtain IRR
 - Potential utility of IRRs to improve health
 - Encourage learning more about their health, change health-related behaviors, share the information with family members, and participate in research studies
- Most wanted as much information as possible Bollinger, J.M., et al. (2012). Public preferences regarding the return of individual genetic research results: findings from a qualitative focus group study. GIM, 14, 451-7

Considerations in the Genomic Era

- >Who is the "patient"
 - Individual AND family AND community
 AND population
 - Can be healthy with only a predicted risk for a health condition or suffering from a health condition
 - Extend across the lifespan
 - Fetus through end of life and beyond

Genetic and Genomic Influences
Across the Healthcare Continuum



Calzone, et al. (2013). Relevance of genomics to healthcare and nursing practice. <u>Journal of Nursing Scholarship</u>, 45, 1-2.

Genomics and the Nursing Workforce

Study	N
National Nursing Workforce Study in collaboration with ANA (NNWF)	619
ANA House of Delegates (HOD)	244
National Coalition of Ethnic Minority Nurses (NCEMNA)	392
Expanding RN Scope of Practice: A Method for Introducing a New Competency into Nursing Practice (MINC)	7347
MINC Admin Only	439

Preconception Prenatal Genetics

> Preconception

- Testing for carrier status prior to pregnancy, often for autosomal recessive disorders
 - •i.e. cystic fibrosis

>Prenatal testing

- Performed during pregnancy
- Indications include
 - Advanced maternal age, increases the risk for chromosomal abnormalities i.e. Down Syndrome
 - Family history of an inherited condition i.e. Duchenne muscular dystrophy
 - Ancestry/ethnic background of parents associated with a higher chance of an inherited disorder

Do YOU know Tracy and David?

As soon-to-be new parents, Tracy and David have a lot of questions. Do they have the right books? The right gadgets? The right name? But thanks to their primary care provider, they don't have questions about their baby's health.

When Tracy and David decided to try to conceive, Tracy visited a new health care provider who took a thorough family history at the first preconception visit. That history revealed that both she and David were of French-Canadian ancestry, putting them at elevated risk of having a baby with Tay-Sachs disease, a lethal inherited disorder affecting the nervous system.

The provider explained the risk to Tracy and David, who chose to undergo genetic counseling and carrier testing. Having learned that they were both carriers of gene alterations that could cause Tay-Sachs, Tracy and David chose to have prenatal genetic testing to determine if their baby would be affected. What a joy to find out that the baby had not inherited Tay-Sachs!

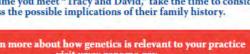
The next time you meet "Tracy and David," take the time to consider and discuss the possible implications of their family history.

To learn more about how genetics is relevant to your practice visit www.genome.gov









Newborn Screening

- Newborn screening consists of a public health approach to the identification and management of health conditions identifiable in the newborn
 - Approximately 4 million newborns screened annually
 - About12,500 new diagnoses as a result of testing
 - Newborn screening constitutes the most extensive use of genetics for public health benefit
 - All states provide newborn screening
- ➤US Secretary of Health and Human Services Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC) provides national guidance about which health conditions should be included

Newborn Screening, cont

- >Health conditions included in newborn screening panels vary by state
- States can opt to include screening for health conditions not recommended by the DACHDNC
- >Health conditions recommended for screening meet the following criteria:
 - Adequate evidence that early diagnosis can improve health outcomes
 - Screening benefits outweigh possibility of harm

Newborn Screening, cont

- Family members may derive benefit from newborn screening even if there is little to no benefit for the newborn
 - Facilitate diagnostic assessments.
 - Inform future reproduction decisions.
 - Prepare for care requirements of the child.
- Newborn screening tests can provide false positive, false negative, or ambiguous results
- Newborn screening is conducted using a dried blood spot from a heel prick.
- Residual dried blood spots can be stored for future uses

Newborn Screening, cont

- Policies for the disposition of dried blood spots and research use vary
- Exploration of next generation genome technologies (i.e., whole genome sequencing) for newborn screening
 - Funding for research exploring this type of technology application is being conducted
 - Plans for management of potential findings, changing evidence base of genetic variations identified and management of incidental findings

Risk Assessment

- More than 55 hereditary cancer syndromes have been identified
- The most common syndromes are those associated with breast, ovarian, and gastrointestinal cancers
 - Tumor features at diagnosis are now being used as an indication for genetic assessment
- >Germline cancer susceptibility gene testing
 - Relevant to individuals diagnosed with cancer whose cancer management may be altered
 - Individuals unaffected with cancer who could benefit from mutation specific cancer risk management
 - At-risk family members

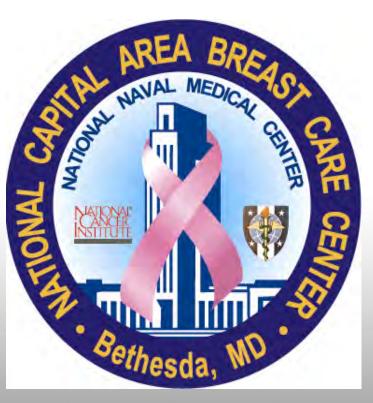
Family History

	In the prior three months nurses seeing patients who RARELY OR NEVER assessed a family history	Took family history: Assessed age at dx	Took family history: Assessed maternal and paternal lineages	AGREED OR STRONGLY AGREED that family history taking should be a key component of nursing care
NNWFS	67%, (n=288/510)	41% (n=200/483)	66% (n=320/484)	84% (n=369/442)
HOD	58% (n=59/102)	51% (n=116/227)	75% (n=168/224)	91% (n=219/242)
NCEMNA	Not Done	64% (n=231/363)	78% (n=280/361)	Not assessed
MINC	69% (n=3270/4774)	29% (n=1564/5348)	53% (n=2850/5336)	71% (n=4051/5701)

Family History, MINC

- ➤ 51.7% (n=2962/5724) reported they were not at all or only a little confident in deciding what family history information is needed to identify genetic susceptibility to common diseases
- ➤ 64.0% (n=3642/5688) reported they were not at all or only a little confident in deciding which patients would benefit from a referral for genetic counseling and possible testing

Family History in Nursing Practice



"It's one of those times in your life that you are grateful you had the knowledge."

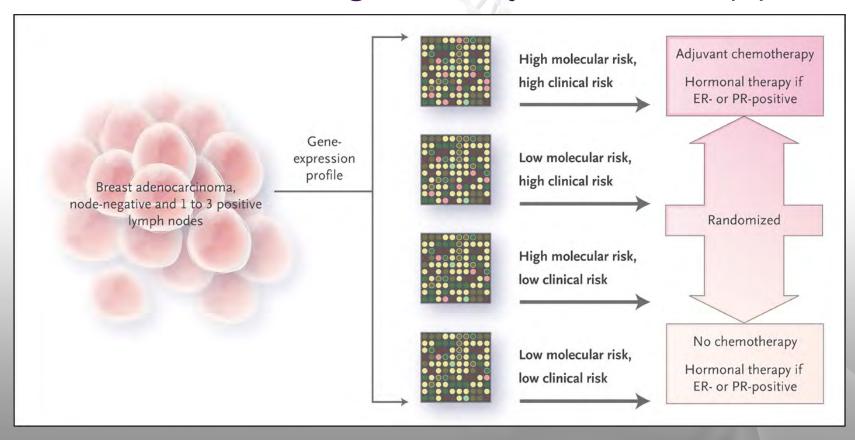
Quote from: Barbara Ganster, RN, BSN Breast Cancer Case Manager National Naval Medical Center

Screening

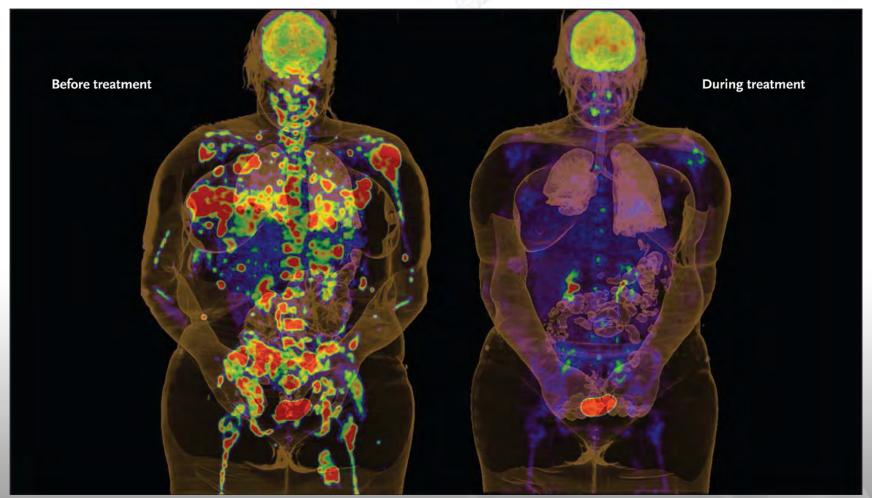
- Genetic information is being used to personalize health screening recommendations
- SNP test results are being studied as a means to increase the specificity of risk calculation models (i.e. Gail model for breast cancer risk)
- Screening tests that include DNA analysis are being developed such as the DNA stool test, a less invasive means to screen for colon polyps or cancer

Diagnosis/Prognosis

- >Establish an accurate diagnosis
- >Tumor profiling is being used to identify recurrence risk to guide adjuvant therapy



Targeting Treatment to a Specific Variant in the Melanoma Gene



McDermott et al. (2011). Genomics and the continuum of cancer care, NEJM, 364, 350-360.

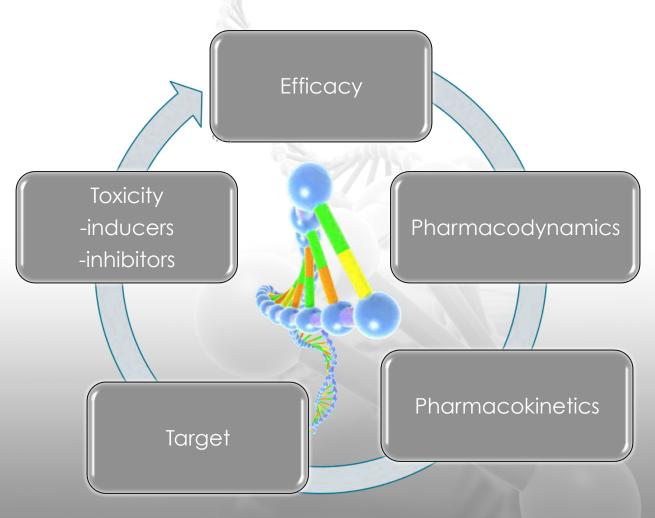


Gene	Genetic Alteration	Tumor Type	Therapeutic Agent
Receptor tyrosine kinase			
EGFR	Mutation, amplification	Lung cancer, glioblastoma	Gefitinib, erlotinib
ERBB2	Amplification	Breast cancer	Lapatinib
FGFR1	Translocation	Chronic myeloid leukemia	PKC412, BIBF-1120
FGFR2	Amplification, mutation	Gastric, breast, endometrial cancer	PKC412, BIBF-1120
FGFR3	Translocation, mutation	Multiple myeloma	PKC412, BIBF-1120
PDGFRA	Mutation	Glioblastoma, gastrointestinal stromal tumor	Sunitinib, sorafenib, imatinib
PDGFRB	Translocation	Chronic myelomonocytic leukemia	Sunitinib, sorafenib, imatinib
ALK	Mutation or amplification	Lung cancer, neuroblastoma, ana- plastic large-cell lymphoma	Crizotinib
c-MET	Amplification	Gefitinib-resistant non–small-cell lung cancer, gastric cancer	Crizotinib, XL184, SU11274
IGF1R	Activation by insulin-like growth factor II ligand	Colorectal, pancreatic cancer	CP-751,871, AMG479
c-KIT	Mutation	Gastrointestinal stromal tumor	Sunitinib, imatinib
FLT3	Internal tandem duplication	Acute myeloid leukemia	Lestaurtinib, XL999
RET	Mutation, translocation	Thyroid medullary carcinoma	XL184
Non-receptor tyrosine kinase			
ABL	Translocation (BCR-ABL)	Chronic myeloid leukemia	Imatinib
JAK2	Mutation (V617F), translocation	Chronic myeloid leukemia, myelo- proliferative disorders	Lestaurtinib, INCB018424
SRC	Overexpression	Non-small-cell lung cancer; ovarian, breast cancer; sarcoma	KX2–391, dasatinib, AZD0530
Serine-threonine-lipid kinase			
BRAF	Mutation (V600E)	Melanoma; colon, thyroid cancer	SB-590885, PLX-4032, RAF265, XL283
Aurora A and B kinases	Overexpression	Breast, colon cancer; leukemia	MK-5108 (VX-689)
Polo-like kinases	Overexpression	Breast, lung, colon cancer; lymphoma	BI2536, GSK461364
MTOR	Increased activation	Renal-cell carcinoma	Temsirolimus (CCI-779), BEZ235
PI3K	PIK3CA mutations	Colorectal, breast, gastric cancer; glioblastoma	BEZ235
DNA damage or repair			
BRCA1 and BRCA2	Mutation (synthetic lethal effect)	Breast, ovarian cancer	Olaparib, MK-4827 (PARP inhibitors)

^{*} PARP denotes poly(adenosine diphosphate-ribose) polymerase.







PK = absorption, distribution, metabolism and excretion PD = mechanism of action, drug concentration and effect

Polymorphisms and Phenotype

UM-Ultrarapid Metabolizer

- Unusually high activity of a drug metabolizing enzyme (DME) or drug transport protein (DTP)
- Limited response to recommended doses

EM-Extensive Metabolizer

- Wild-type (normal activity) form of a DME or DTP
- Expected efficacy at recommended doses

IM-Intermediate Metabolizer

- Reduced activity of a DME or DTP
- Some decreased efficacy at recommended doses

PM-Poor Metabolizer

- Very low or no activity of a DME or DTP
- Increased toxicity
- Decreased efficacy at recommended doses

Katz et al. (2008). Defining drug disposition determinants: A pharmacogenetic-pharmacokinetic strategy. Nature Reviews Drug Discovery, 7, 293-305.

Inhibitors and Inducers

Inhibitors

 Reduce the drug metabolizing enzyme or drug transport protein

· Inducers

 Increase the drug metabolizing enzyme or drug transport protein

Symptom Management

- >Priority area of nursing research is the study of the genetic influences of symptom clusters
- >Pharmacogenomics
 - Inhibitors and/or Inducers
 - Implications for:
 - Medications used for other health conditions
 - Selecting medications to control
 - Use of over the counter medications like St. Johns'
 Wort
 - Consumption of certain foods or supplements like grapefruit/grapefruit juice



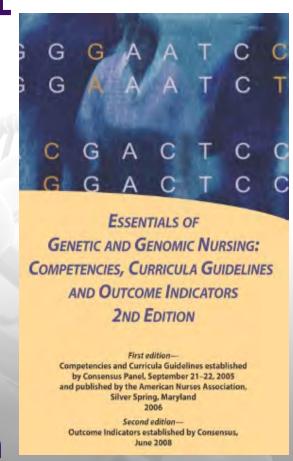
The Quest for Personalized Health Care

- >Use of an individual's genetic/genomic information In addition to traditional health information to guide health care decision-making
- Disease prevention, risk reduction, diagnosis, treatment, symptom management and palliative care
 - Pharmacogenomics
 - Medication selection
 - Dose selection
 - Inhibitors
 - ·Inducers

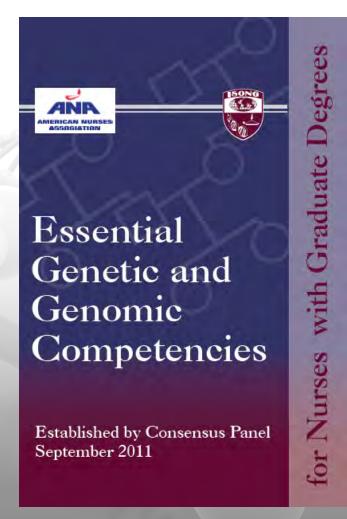
Essentials of Genetic and Genomic Nursing

Define essential genetic and genomic competencies for **ALL** nurses regardless of level of academic preparation, practice setting or specialty

- Endorsed by 50 nursing organizations
- October 22-24 2006 Strategic Implementation Meeting
- >2nd Edition incorporated Outcome Indicators
 - Specific Areas of Knowledge
 - Clinical Performance Indicators
- >3rd Edition may be published in 2013 which includes some updates



- Define essential genetic and genomic competencies for **ALL** graduate nurses regardless of level of academic preparation, practice setting or specialty.
- Established by a process of consensus



Genomic Knowledge

	Rate their understanding of the genetics of common diseases as EXCELLENT or VERY GOOD	Have heard or read about the Genomic Nursing Competencies
NNWFS	14% (73/510)	32.7% (166/506)
MINC	5% (276/5100)	9% (n=453/5021)
Cancer Center	13% (n=8/61)	27% (n=18/66)

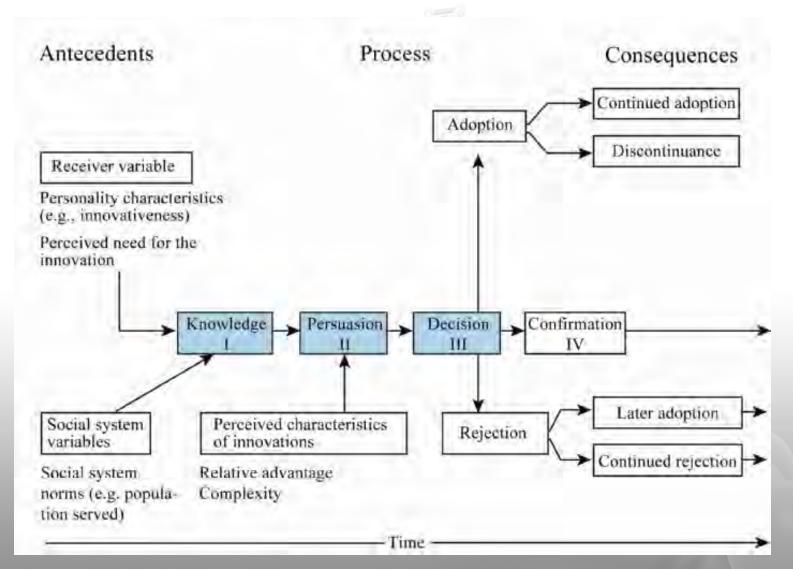
Objective Measure of Knowledge and Competency

- ➤Total Knowledge Score
 - 12 knowledge/competency questions
 - Correct or incorrect
 - Total Knowledge Score calculations done on ONLY those who answered ALL 12 questions

Total Knowledge Scores

	6-30			
	Total knowledge score was calculated from 12 knowledge questions	CORRECTLY answered question about whether genomic risk (as indicated by Fm Hx) has clinical relevance for coronary heart disease	INCORRECTLY stated that diabetes and heart disease are caused by a single gene variant	
NNWFS	8.99/12, Range 1-12, SD 1.69	99% (n=437/442)	61% (n=268/442)	
HOD	9.24/12, range 3-12, SD 1.50	98% (n=216/220)	62% (n=137/220)	
NCEMNA	Not Done	74% (n=275/274)	66% (n=92/138)	
MINC	8.09/12, range 0-12, SD 1.62	82% (n=4116/5118)	71% (n=3580/5008)	
MINC Admin	Not Done	89% (n=386/434)	76% (n=330/435)	

Diffusion of Innovations



Adopted from: Rogers, Everett M. (2003). Diffusion of Innovations, Fifth Edition. New York, NY: Free Press

Genomic Attitudes

	Reported it was SOMEWHAT OR VERY IMPORTANT for nurses to become more educated about genetics of common disease	Believe senior staff see genetics as an IMPORTANT part of the survey respondent's personal role	WOULD attend a genetics course on their own time
NNWFS	92% (n=572/607)	Not assessed	73% (n=368/506)
HOD	98% (n=239/244)	Not assessed	75% (n=182/240)
NCEMNA	97% (n=374/385)	24% (n=87/359)	Not Assessed
MINC	89% (n=5992/6741)	26% (n=1302/5110)	64% (n=3248/5087)
MINC Admin	93% (n=406/438)	27% (n=118/431)	68% (n=294/433)

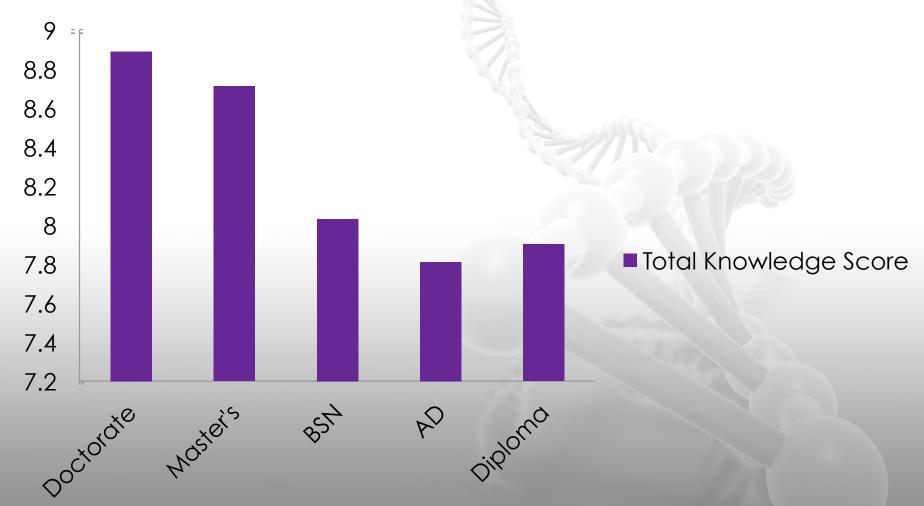
Clues to Educational Needs

Most:

- Indicate a potential disadvantage to integrating genomics into practice was that it would increase insurance discrimination
- Felt that genetics could increase patient anxiety about risk, despite behavioral studies in many conditions indicating that most patients do well with genetic information.
- >Felt genetics is not reimbursable or too costly
- >Feel genetics is important BUT do not think that senior staff feel it is important to their role
- Are willing to learn more, and are willing to do so on their own time

Overall Education Impact

Total Knowledge Score By Highest Level of Nursing Education



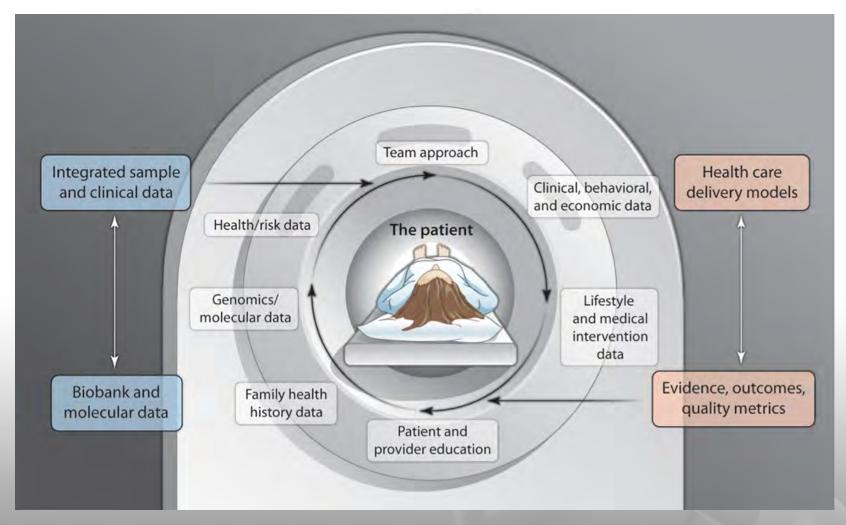
Genetic Education Impact

	Prior Genetics Education	No Prior Genetics Education	P-value
Reported hearing or reading about the Competencies	24.9%	6.4%	<0.001
Self described genetic/genomic knowledge and Good/Fair	44.6%	29.5%	<0.001
Mean age of nurses reporting genetics in their curriculum	41.8 years	46.1 years	<0.001

Potential Policy Implications

- > Regulatory
 - Guidance to IRBs and researchers using whole genome analysis
- >MINC Participant Policy Initiatives
 - Genetic education, counseling and informed consent for genetic tests
 - Pathways for referrals to genetic services
 - Documentation of family history
 - Genomic Nursing Competency
- >MINC Existing Policies
 - Genomic Advanced Directives

Personalized Health Care Requirements



Ginsburg G S et al. Sci Transl Med 2011;3:101cm27-101cm27



State of the Science Initiative

- Establish a blueprint for genomic nursing science that can be used to focus research efforts to fill identified evidence gaps
- >Establish the blueprint through
 - Analysis of the evidence
 - Expert evaluation of the current state of the science
 - Public comment

Methods

- State of the Science Advisory Panel Convened
- >Evidence Reviews
- > Meetings
 - Interactive Webinars (2)
 - In-person meetings (2)
- >Public Comment

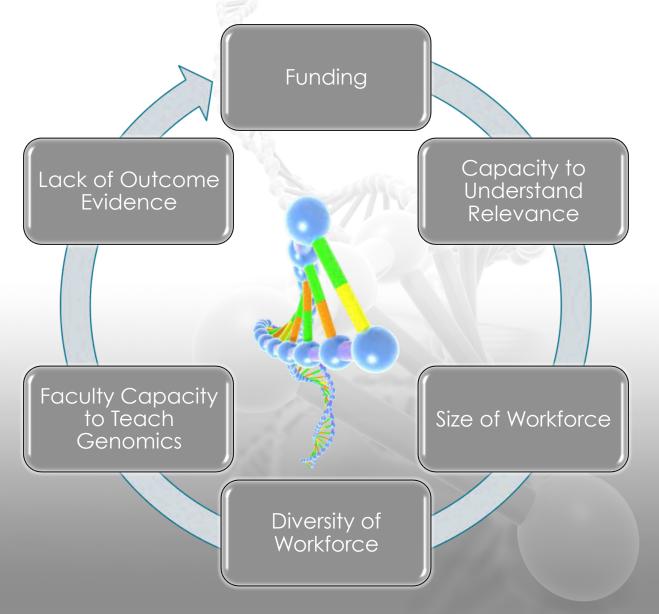
Genomic Nursing State of the Science Advisory Panel, Calzone, K., Jenkins, J., Bakos, A.D., Cashion, A., Donaldson, N., Feero, W.G., Feetham, A., Grady, P.A., Hinshaw, A.S., Knebel, A.R., Robinson, N., Ropka, M., Seibert, D., Stevens, K.R., Tully, L.A., Webb, J.A. A blueprint for genomic nursing science. <u>Journal of Nursing Scholarship</u>, 45, 96-104

Advisory Panel Conclusions

- >Focus on research producing clinically evidence along the translation science continuum
 - Use multifacted methodologies and measurements
 - Build on existing work
- >Framework is NINR Strategic Plan Areas
- Clients definition consistent with Genomic Nursing Competencies
 - Persons, families, communities, and/or populations
- >Two major research areas
 - Focus on the Client
 - Focus on the context in which health care is delivered
- >Cross cutting themes

http://www.ninr.nih.gov/sites/www.ninr.nih.gov/files/jnu_12007_Rev_EV.pdf http://www.genome.gov/27552093

Challenges and Opportunities



Resources

- >Journal of Nursing Scholarship Genomic Special Issue
 - Webinar Series with Issue Authors http://www.genome.gov/27552312
- Genetics/Genomics Competency Center for Education (G2C2) http://www.g-2-c-2.org
- CDC Public Health Genomics http://www.cdc.gov/genomics/
- >Genomic Competency Listserv Email: calzonek@mail.nih.gov

Resources, continued

Global Genetics and Genomics Community

http://www.g-3-c.org

>NHGRI and Smithsonian collaborative exhibit

Genome: Unlocking Life's Code Museum of Natural History http://unlockinglifescode.org/

ISONG is Celebrating 25 Years!



Conference Dates

October 4-6, 2013

Conference Hotel

DoubleTree by Hilton Bethesda, Maryland USA

Abstracts Accepted

March 1 - April 8, 2013

For More Information Visit

www.isong.org

Summary

- Recognize the relevancy and value of genomics to your responsibilities
- >Utilize your leadership and skills to be a change agent/champion in your healthcare environment
- Recognize policy opportunities to ensure safe, effective and efficient translation of genomic clinical care
- >Think creatively and be innovative about designing services, staff education, clinical infrastructure (i.e., EHR) that facilitates adoption of genomics in care
- ➤ Visualize how you can leverage interprofessional teams to assure that all healthcare providers are adequately prepared to be able to transform healthcare delivery

Questions/Discussion

calzonek@mail.nih.gov 301-435-0538

